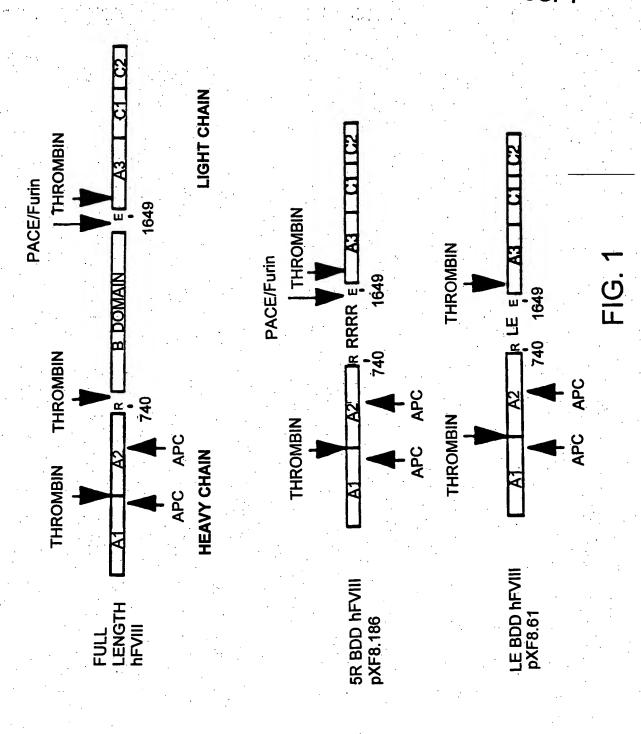
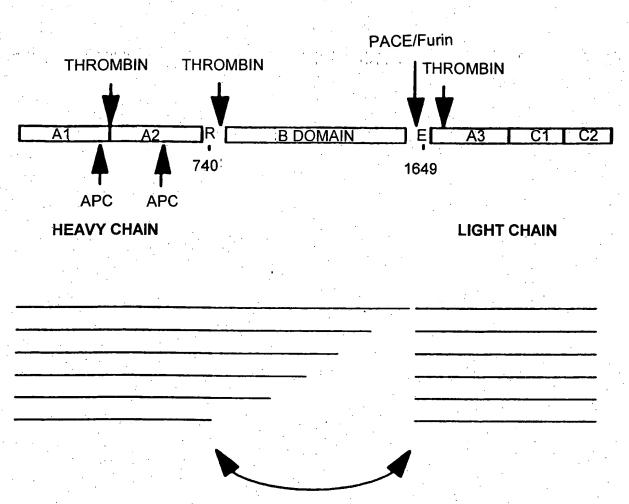
### Page 1 of 33 OPTIMIZED MESSENGER RNA 09/407,605 10278-009001 REPLACEMENT SHEET

### BEST AVAILABLE COPY



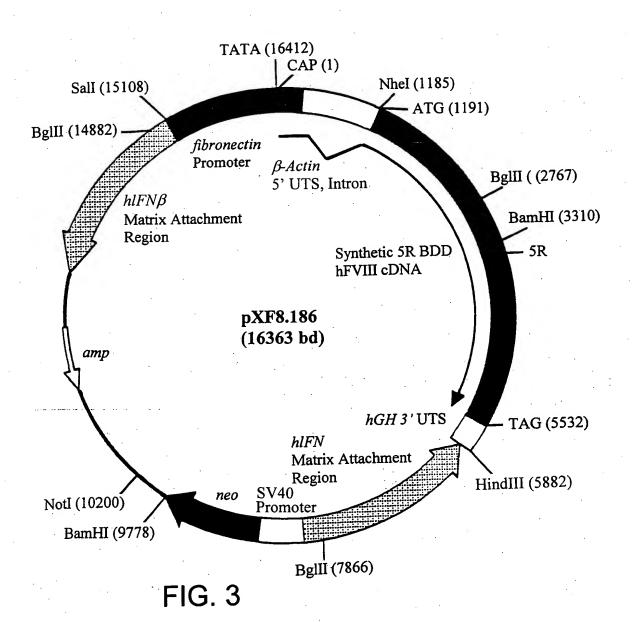
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HETEROGENEITY OF hFVIII IS DUE TO PROTEOLYSIS WITHIN THE B-DOMAIN

FIG. 2



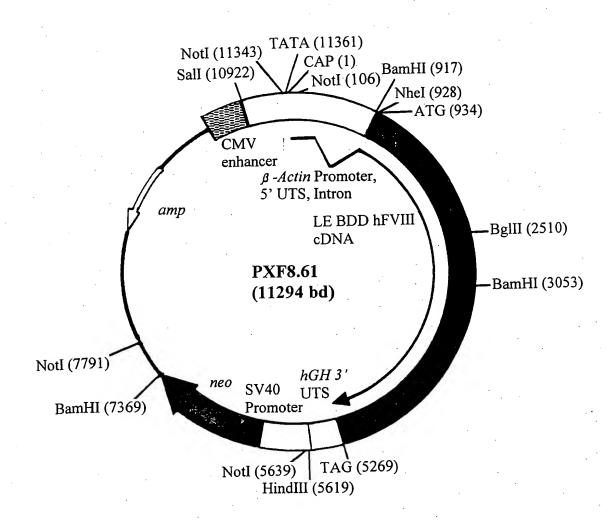


FIG. 4

# Fragment A

Nhel

**AM1 Af1** 

GTAGAATTCGTAGGCTAGCATGCAGATCGAGCTGAGCACCTGCTTCTTCCTGTGCCTGCTGCGCTTCTGC

AM1 Ar3

3, OH 5, P

3. OH

AM1 Af2

AM1 Ar2

CCCGCTCGACGGGCACCTGCGGGGGGGGGGGGGCGCACGGGTTCTCGAAGG GGAAGTTGTGGTCGCA GGGCGAGCTGCCCGTGGACGCCCGCTTCCCCCCCCCGCGTGCCCAAGAGCTTCCTCCTTCAACACCAGCGT

3, OH 5, P

AM1 Af3

GGTGTACAAGAAGAC CCTGTTCGTGGAGTTCACCGACCACCTGTTCAACATCGCCAAGCCCCGCCCCCC 

**AM1Ar1** 

Apal

Hud

CTGGATGGGCCTGCTGGGCCCC TACAAGCTTTAC GACCTACCCGGACGACCCGGGGATGTTCGAAATG

FIG. 5A

## Fragment B

GTAGAATTCGTAGGGGCCCCACCATCCAGGCCGAGGTGTACGACACCGTGGTGATCACCCTGAAGAACATGGCCAG CATCTTAAGCATCCCCGGGGTGGTAGGTCCGGCTCCACATGCTGGGCACCACTAGTGGGGACTTCTTGTACCGGTC AM1Bf1

AM1.Br3

3. OH 5' P

Geregegeactice eacerecegeaccegeactegateac\_critecegicectecegegetearecregeter CCACCCGTGAGC TTGCACGCCGTGGGCGTGAGCTACTG GAAGGCCAGCGAGGGCGCCGAGTACGACGACAGA

5. P 3. OH

AM1 Br2

3. OH 5. P

ccagccagcgagaaggacgacaaggtgttccccgg~cggcaccaccacctacgtgtggcaggtg ctgaag GGTCGGTCGCGCTCTTCCTCTTCCACAAGGGGCC GCCGTCGGTGTGGATGCACACCGTCCAC\_GACTTC

5. P 3. OH AM1Bf2

AM1Bf3

PmI

CTCTTGCCGGGGTACCGGTCGCTGGGGGACACGGACTGGATGTCGATGGACTCGGTGCACGATGTTCGAAATG GAGAACGGCCCCATGGCCAGCGACCCCCTGTGCCTGACCTACAGCTACCTGAGCCACGTGCTACAAGCTTTAC

AM1 Br1

FIG. 5B

# Fragment (

GTAGAATTCGTAGCCACGTGGACCTGGTGAAGGACCTGAACAGCGGCCTTGATCGGCGCCCTGCTGGTGTGCCGCGAGGGCAGCCTG CATCTTAAGCATCGGTGCACCTGGACCTTCCTGGACTTGTCGCCGGACTAGCCGCGGGACGACCACACGGCGCTCCCGTCGGAC PmI EcoRi

AM1C11

AM1 Cr3

3. OH 5. P

AM1 Cf2

cggttcctcttctq ggtctgggacgtgttcaagtag\_gacgacaaggggcacaagctgctcccgttctcgaccgtgtcgctcttgg GCCAAGGAGAAGAC TCAGACCCTGCACAAGTTCATC CTGCTGTTCGCCGTGTTCGACGAGGGCAAGAGCTGGCACAGCGAGACC

3. OH 5. P

AAGAACAGCCTGATGCAGGACCGCGACGCCCCAGCGCCCTGGCCCCAAGATGCACAC CGTGAACGGCTACGTGAACCGC TICTIGICGACTACGICCTGCGCGCGGCGGTCGCGGG CGCGGACCGGGTICTACGIGIGGCACTIGCCGAIGCACTIGGCG

Hugh Find Pml FIG. 5C

AM1Cf3

**AGCCTGCCCGGCCTGATCGGCTGCCACGCAAGAGCGTGTACTGGCACGTGCTACAAGCTTTAC** TCGGACGGCCGGACTAGCCGACGGTGCGTTCTCGCACATGACCGTGCACGATGTTCGAAATG

AM1C1

## Fragment

GTAGAATTCGTAGCACGTGATCGGCATGGGCACCACCCCCGAGGTGCACAGCATCTTCCTGGAGGGCCACACTCTTCCTGGTGCGCAACCACCG AM1Df1 PmI <u>E89</u>

CATCTTAAGCATCGTGCTACCCGTGGTGGGGGGCTCCACGTGTCGTAGAAGGACCTCCCGGTGTG GAAGGACCACGCGTTGGTGGC AM1Dr4 SY P 3' OH AM1Df2 3. OH 5. P

CCAGGC CAGCCTGGAGATCAGCCCCATCACCTTCCTGACCGCCCAGACCCTGCTGATGGACCTGGGCCAGTTCCTGCTGTTTTTGCCACATCA

GGTCCG\_GTCGGACCTCTAGTCGGGGTAGTGGAAGGACTGGGGACGACTACCTGGACCGGTCAAGGACGACAA GACGGTGTAGT
AM1Dr3
5' P 3' OH gcagccaccagcac dacgecatggaggcctacgtgaaggtggacagctgccccgaggagggccccagctgcgcatgaagaacaacgaggagg Tc **AM1Df3** 3. OH 5' P

BamH GAGGACTACGACGACGACCTGAC CGACAGCGAGATGGACGTGGTGCGTTCGACGACGACAACAGCCCCAGCTTCATCCAGATCTCTACGGAT AM1Df4 AM1Dr2 3. OH 5' P

CTCCTGATGCTGCTGCTGGACTG\_GCTGTCGCTCTACCTGCACCACGCGAAGCTGCTGTTGTCGGGGTCGAAGTAGGTCTAGAGATGCCTA AM1Dr1

CCTACAAGCTTTAC GGATGTTCGAAATG

## Fragment E

**元**80元

BamHI

CATCTTAAGCATCCCTAGGCGTCGCACCGGTTCTTCGTGGGGTTCTGGACCCACGTGATGTAGCGGCGGCTCCTCCTCCTGACCCTGATGTGCG GTAGAATTCGTAGGGATCCGCAGCGTGGCCAAGAAGCACCCCAAGACCTGGGTGCACTACATCGCCGCCGAGGAGGAGGACTGGGACTACGC

**AM1Ef1** 

AM1Er4

3, OH 5' P

cccctg Grectegecccccgacgacgccda cracaagaccagraccrgaacaacgcccccagcgcarcgccaagcgaagracaaga GGGGGAÇ ÇACGACCGGGGGCTGCTGGCGTC\_GATGTTCTCGGTCATGGACTTGTTGCCGGGGGTCGCGTAGCCGGCGTTCATGTTCTTCCA AM1Er3

**AM1Ef2** 

3'OH 5'P

CGCGAAGTACCGGATGTGGCTGCTCTGGAAGTTCTGGG CGCTCCGGTAGGTCGTGCTCTC\_GCCGTAGGACCCGGGGGACGACATGCCGCT GCGCTTCATGGCCTACACCGACGAGACCTTCAAGACCC GCGAGGCCATCCAGCACGAGAG CGGCATCCTGGGCCCCCTGCTGTACGGCGA Apal

AM1Ef3

5. P 3. OH

3. OH 5. P

ggigggcgacacccigctgatcatcitcaagaaccaggccagccgccctacaacaictacc CCACCCGCTGTGGGACGACTAGTAGAAGTTCTTGGTCCGGTCGGGGGATGTTGTAGATGG GGGTGCCGTAGTGGCTGCACGCG\_GGGGA

AM1E2

CATGTCGGCGGCGGACGGGTTCCCGCACTTCGTGGACTTCCTGAAGGGGTAGGACGGGCCGCTCTAGAGATGTTCGAAATG GTACAGCCGCCGCCTGCCCAAGGGCGTGAAGCACCTGAAGGACTTCCCCATCCTGCCCGGCGAGATCTCTACAAGCTTTAAC

AM1Ef4

AM1E1

FIG. 5E

## Fragment

CATTICGAACATCCCATGGTCGACGCCAAGAGCAGCTTGTGCGACTTGTCCTAGTGCAACG CGAACAGCGAGTACTAGACCAACGG ATTICGAACAACGG S' OH 

AM1F11

Kpnl

Hindill Hindill

3'OH 5'P AM1 Ff2 decreerce control of conference of confer 

**AM1 Fr2** 

BgIII

CTGTAGTAGCGGGTCAG GCAGCGGGGTCGCTCTTGGTGGGGCCGTCCTCCACGGTCACGGTCCACTTGTACTTGAAGATCTCTAC GACATCATCGCCCAGTC\_CGTCGCCCCCAGCGAGAACCACCCCGGCAGGAGGTGCCAGTGCCAGGTGAACATGAACTTCTAGAGATG AM1Ff3 3. OH 5' P

AM1 Fr1

ESSH

GAATTCTAC CTTAAGATG

# Fragment G

Kpnl ESSE

**AM1Gf1** 

GTAGAATTCGTAGGGTACCTGACCGAGAACATCCAGCGCTTCCTGCCCAACCCCGGCGTGCAGCTGGAGGACCCCCGAGTTCCAGGCCAG CATCTTAAGCATCCCATGGACTGGCTCTTGTAGGTCGCGAAGGACGGGTTGGGGCGGCCGCACGTCGACCTCCTGGGGCTCAAGGTCCGGTC

**AM1Gr3** 

3. OH 5' P

CAACAT CATGCACAGCATCAACGGCTAC GTGTTCGACAGCCTGCAGCTGAGGGTGCCTGCAGGTGGCCTACTGGTACATCCTGAG GTTGTA GTACGTGTCGTAGTTGCCGATG\_CACAAGCTGTCGACGTCGACTCGCACACGGACGTGCTCCACCGGATGACCATGTAGGACTC AM1Gf2 **AM1Gr2** 5, P 3, OH

3. OH 5' P

GTAGCCGCGCGCTCTGGCTCAAAGACTCGCACAAGAAGTCG ÇCGATGTGGAAGTTCGTGTTCTAC\_CACATGCTCCTGTGGGACTGGGACAA CATCGGCGCCCAGACCGACTTCCTGAGCGTGTTCTTCAGCTGGCTACACCTTCAAGCACAAGATG GTGTACGAGGACACCCTGACCTGTT 5. P 3. OH

AM1Gf3

BamHI

GGGGAAGTCGCCCCTCTGGCACAAGTACTCGTACCTCTTGGGGCCGGACACCTAGGGATGTTCGAAATG CCCCTTCAGCGCGAGACCGTGTTCATGAGCATGGAGAACCCCGGCCTGTGGATCCCTACAAGCTTTAC AM1Gr1

FIG. 5G

# Fragment H

CATCTTAAGCATCCCTAGGACCCGACGGTGTTGTCGCTGAAGGCGTTTGGCGCCGTACTGGCGGGACGACTTCCACTCGTCGAÇ GCTGTTCTTGTGGCCGCTG GTAGAATTCGTAGGGATCCTGGGCTGCCACAACAGCGACTTCCGCAACCGCGGCATGACCGCCCTGCTGAAGGTGAGCAGCTGTCGACAAGAACACCGGCGAC **AM1Hf1** BamHI ESSE

AM1Hr4

CGACCAGGAG GAGATCGACTACGACGACACCATCAGCGTGGAGATGAAGAAGGAGGACTTCGACATCTACGAGGACGAGGACGAGAACCAGAGCCC^CCGCAGCT GCTGGTCCTC\_CTCTAGCTGATGCTGCTGTGGTAGTCGCACCTCTACTTCTTCCTCTGAAGCTGTAGATGCTGCTCCTGCTCTTGGTCTCGGG GGCGTCGA ATGATGCTC\_CTGTCGATGCTCCTGTAGTCGCGGATGGACGACTCGTTCTTGTTGCGGTAGCTCGGGGCGGACCTCCTCTAGTGGGCGTG GTGGGACGTCTC AM1Hf3 AM1Hr3 3. OH 5. P

**AGGTCTTCTTCTGG\_GCGGTGATGAAGTAGCGGCGCGCACCTCGCGGACACCCTTGATGCCGTACTCGTCGGGGGTGCACGATGTTCGAAATG** AM1Hr1

**AM1Hr2** 

-1G. 5F

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## Fragment

	동
AGGAGTTCACCGACGCAG CTTCACCCAG PCCTCAAGTGGCTGCGTC GAAGTGGGTC 5'P 3'OH	Bst EII ACATCATGGTGACCGTGCAGGAGTTCG TC IGTAGTACCACTGGCACGTCCTCAAGC GG 5' P 3' OH
AM1 If 1 gtgccccagttcaagaaggtggttcca cacggggtcaagttcttccaccacaaggt	AM1 If 2 ccctacatccgcgccgaggtggaggacaa gggatgtaggcgcggctccacctcctgty
Emri Pmii gtrgratticgtagcacgtgctgcgcgcgcgcggggggggggggg	3' OH 5' P  ccctgtacce deceaecteaaceaectectectegecetectacatecegegecegegegegegegegegegegegegegegege
Ecori GTAGAATTCGTAGCACG CATCTTAAGCATCGTGC	3'OH 5'P ccccrgraccec decc ggggacarggcg_ccgc

 AM1 If 3	ctgitcitcaccatcitcada dagaccaagagctggtactitcaccgagaacatgggggggggg	
3. OH 5. P	ctgitcitcaccatcitcaac dagaccaagagetggiacticacca gacaagaagtggiagaagctg_ctctggttctcgaccatgaagtggct AM1 Ir2	

3' OH 5' P
TICAAGGAGAACTACCGCTTCCACG CCATCAACGGCTACATCATGGACACCTGCCCGGCCTGGTGATGGCCCAGGACCAGCGCATCCGCTGGTACCTAACAA
AAGTTCCTCTTGATGGCGAAGGTGC\_GGTAGTTGCCGATGTAGCTTACTGGACCGGCCCACCACGGTCCTGGTCGCGAAGGCGACCATGGGATGTT AM1 If 4 AM1 lr1

GCTTTAC CGAAATG

## Fragment

**Bst Ell** ExoRi

AM1 Jf

GTAGAATTCGTAGGGTGACCTTCCGCAACCAGGCCAGCCGCCCCTACAGCTTCTACAGCAGCCTGATCAGCTACGAGGAGGACCAGCGCC CATCTTAAGCATCCCACTGGAAGGCGTTGGTCCGGTCGGCGGGGATGTCGAAGATGTCGTCGGACTAGTCGATGCTCCTCCTCGTCGCGG

AM1 Jr3

3. OH 5. P

AM1 Jf2

AGG GCGCCGAGGCCCCGCAAGAACTTC GTGAAGCCCAACGAGACCAAGACCTACTTCTGGAAGGTGCAGCACCACATGGCCCCCACCAA TCC CGCGCTCGGGGCGTTCTTGAAG\_CACTTCGGGTTGCTCTGGTTCTGGATGAAGACCTTCCACGTCGTGGTGTACCGGGGGTGGTT a, OH

AM1 Jr2

3'OH 5'P GGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCAG CGACGTGGACCTGGAGGAGGAC GTGCACAGCGGCCTGATCGGCCCCCTGCTG CCTGCTCAAGCTGACGTTCCGGACCCGGATGAAGTÇ GCTGCACCTGGACTTCCTG\_CACGTGTCGCCGGACTAGCCGGGGGACGAC

Eagl AM1Jf3

**Bst Ell** 

Hud

GTGTGCCACACCAACACCCTGAACCCCCGCCCACGGCCAGGTGACCCTACAAGCTTTAC 

# Fragment K

Kpnl Ewall

Pm **AM1Kf1** 

CATCTTAAGCATCCCATGGACGACTCGTACCCGTCGTTGCTCTTGTAGGTGTGGAGGTGAAGTCGCCGGTGCACAAGTGGCACGCGTTCTT GTAGAATTCGTAGGGTACCTGCTGAGCATGGGCAGCAACGAGAACATCCACAGCATCCACTTCAGCGGCCACGTGTTCACCGTGCGCAAGAA

AM1Kr3

3. OH 5. P

**AM1Kf2** 

GGAG GAGTACAAGATGGCCCTGTACAAC CTGTACCCCGGCGTGTTCGAGACCGTGGAGATGCTGCCCAGCAAGGCCGGCATCTGGCGCGT CCTÇ ÇTCATGTTCTACCGGGACATGTTG\_GACATGGGGCCGCACAAGCTCTGGCACCTCTACGACGGGTCGTTCCGGCCGTAGACCGCGCA **AM1Kr2** æ, oH, ы 2

CCTCACGGACTAGCCGCTCGTGGACGTGCGGCCGTACTÇ GTGGGACAAGGACCACATGTC\_GTTGTTCACGGTCTGGGGGGACCCGTACCG 3'OH 5'P GGAGTGCCTGATCGGCGAGCACCTGCACGCCAGGCATGAGTCACCTGTTCCTGGTGTACAG CAACAAGTGCCAGACCCCCTGGGCATGGC 5, P 3, OH

AM1Kf3

IIpuII Apai

CAGCGGCCACATCCGCGACTTCCAGATCACCGCCAGCGGCCAGTACGGCCCAGTGGGCCCCTACAAGCTTTAC GTCGCCGGTGTAGGCGCTGAAGGTCTAGTGGCGGTCGCCGGTCATGCCGGTCACCCGGGGGATGTTCGAAATG

FIG. 5X

## Fragment

GTAGAATTCGTAGGGCCCCCCAAGCTGGCCCGCCTGCACTACAGCGCAGCATCAACGCCTGGAGCACCAAGGAGCCCTTCAGCTGGATCAAG CATCTTAAGCATCCCGGGGGTTCGACCGGGCGGACGTGATGTCGCCGTCGTAGTTGCGGACCTCGTGGTTCCTCGGGAAGTCGACCTAGTTC

**AM1Lr3** 

GTGGAC TTGCTGGCCCCCATGATCATC CACGGCATCAAGACCCAGGGCGCCCGCCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCA CACCTG GACGACCGGGGGTACTAGTAG\_GTGCCGTAGTTCTGGGTCCCGCGGGCGGTCTTCAAGTCGTCGGACATGTAGTCGGTCAAGTAGT 3 OH

AM1Lr2

3. OH 5. P

TCATGTACAGCCTGGACGGCAAGAAGTG GCAGACCTACCGCGGCAACAGCAC CGGCACCCTGATGGTGTTCTTCGGCAACGTGGACAGCAG AGTACATGTCGGACCTGCCGTTCTTCAC CGTCTGGATGGCGCCGTTGTCGTG\_GCCGTGGGGACTACCACAAGAAGCCGTTGCACCTGTCGTC

Smal AM1Lf3

GCCGTAGTTCGTGTTGTAGAAGTTGGGGGGGCCCCGATGTTCGAAATG CGGCATCAAGCACAACATCTTCAACCCCCCCGGGCTACAAGCTTTAC

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# Fragment M

ESO F E82

**AM1Mf1** 

**AM1Mr3** 

3. OH 5. P

**AM1Mf2** 

GACGCTG GACTTGTCGACGTCGTACGGGGACC\_CGTACCTCTCGTTCCGGTAGTCGCGGGGTCTAGTGGCGGTCGTCGATGAAGTGG CTGCGAC TTGAACAGCTGCAGCATGCCCCTGG GCATGGAGAGACCAATCAGCGACGCCCAGATCACCGCCAGCAGCTACTTCACC 5 P 3 OH

3' OH 5' P

AACATGTTCGCCACCTGGAGCCCCAGCAAGGCCTCGCCTGCAGGCCGCAG CAACGCCTGGCGCCCCCAGGTGAACAACCCCA TTGTACAAGCGGTGGACCTCGGGGTCGTTCCGG GCGGACGTGGACGTCCCGGCGTC\_GTTGCGGACCGCGGGGGTCCACTTGTTGGGGGT

5, P 3, OH

**AM1Mf3** 

Bst Ell

Hud

AGGAGTGGCTGCAGGTGGACTTCCAGAAGACCATGAAGGTGACCCTACAAGCTTTAC TCCTCACCGACGTCCACCTGAAGGTCTTCTGGTACTTCCACTGGGATGTTCGAAATG

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Smal

Fragment N

**Bst EII** E89E

**AM1Nf1** 

GTAGAATTCGTAGGGTGACCGGCGTGACCAGGGCGTGAAGAGCCTGCTGACCAGCATGTACGTGAAGGAGTTCCTGATCAGCAGCAGCAGCCAGGACGG TCCA

3. OH 5. P

**AM1Nf2** 

CCAGTGGACCCTGTTCTTC CAGAACGGCAAGGTGTTCCAGGGCAACCAGGACAGCTTCACCCCCGTGGTGAACAGCCTGGACCCCCCCTGTCTGAC

**AM1Nf3** 

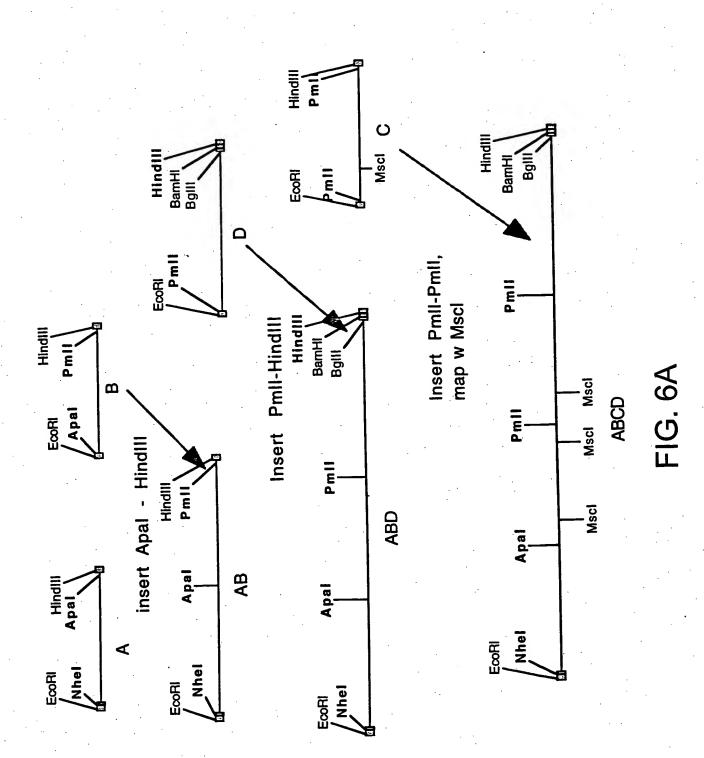
GGCGATGGACGCGTAGGTGGG\_GGTCTCGACCACGTGGTCTAGCGGGACGCGTACCTCCACGACCCCGACGCTCCGGGTCCTGGACATGATCGACGGGCCCGAT 

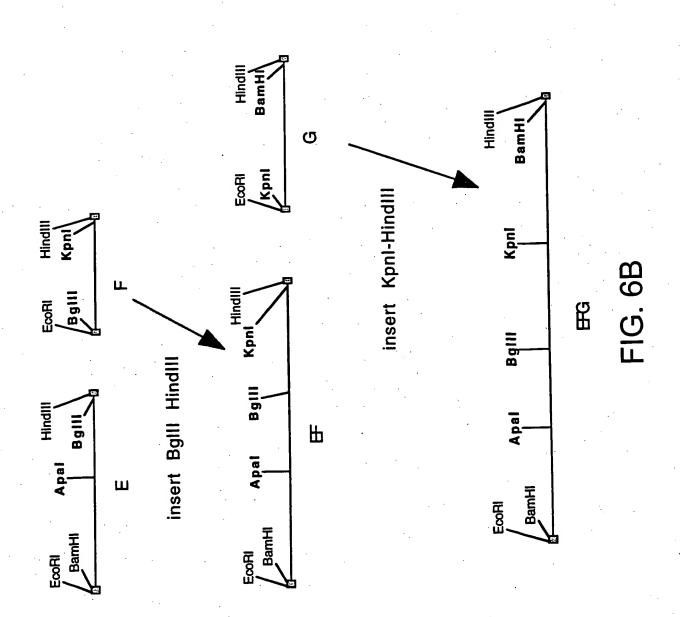
3. OH 5' P

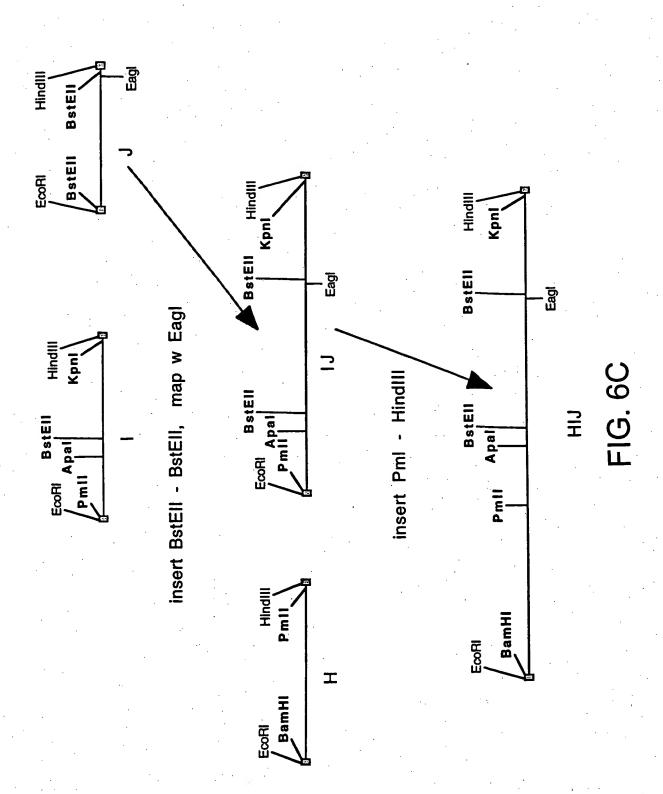
**AM1Nr1** 

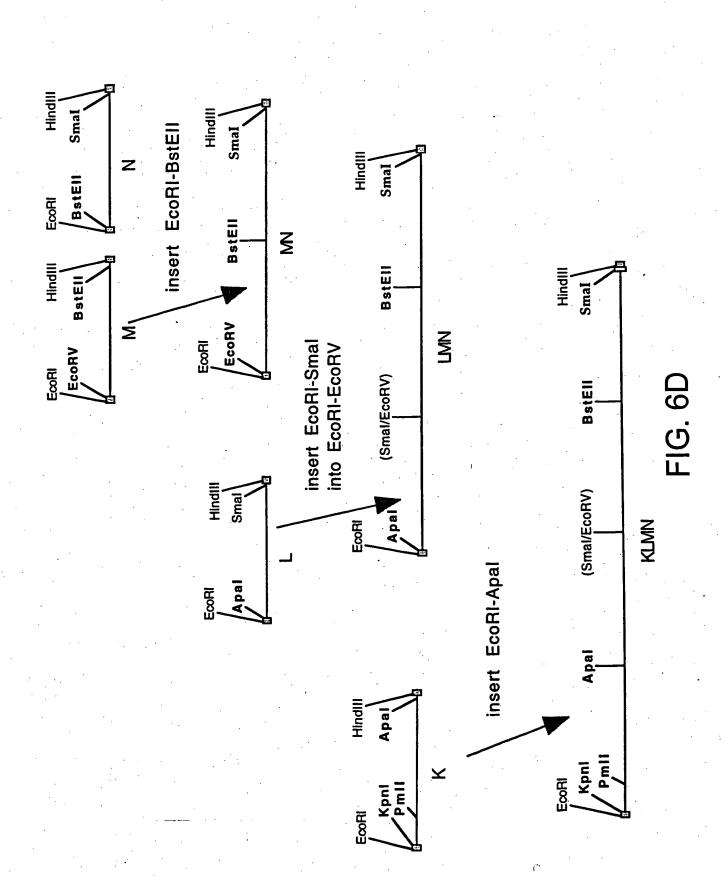
Hindill

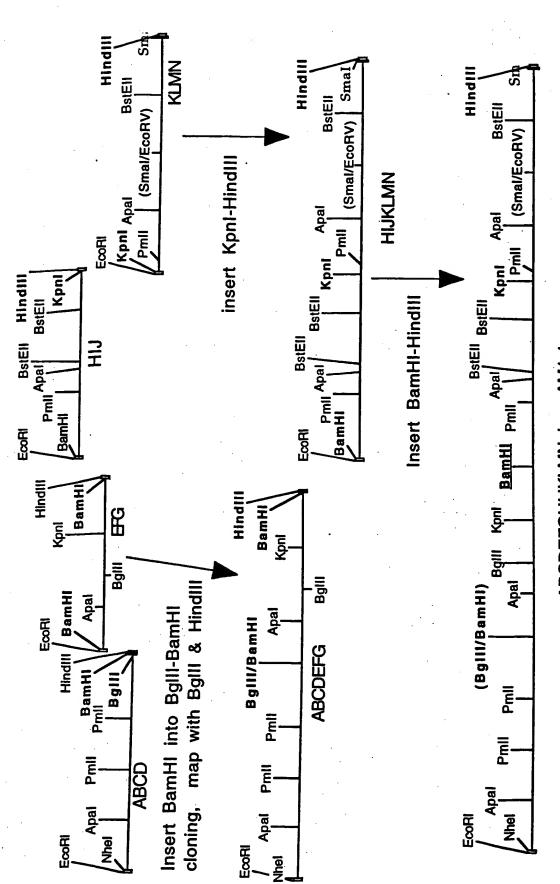
CAAGCTTTAC GTTCGAAATG











ABCDEFGHIJKLMN, i.e. pAM1-1

FIG. 6E

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	EcoRI Nhei
1	TAGAATTCGTAGGCTAGCATGCAGATCGAGCTGAGCACCTGCTTCTTCCTGTGCCTGCTGCGCTTCTGCTTC
_	1 MetGlnIleGluLeuSerThrCysPhePheLeuCysLeuLeuArgPheCysPhe
73	AGCGCCACCCGCCGCTACTACCTGGGCGCCGTGGAGCTGAGCTGGGACTACATGCAGAGCGACCTGGGCGAG
19	SerAlaThrArgArgTyrTyrLeuGlyAlaValGluLeuSerTrpAspTyrMetGlnSerAspLeuGlyGlu
145	CTGCCCGTGGACGCCCGCTTCCCCCCCCGCGTGCCCAAGAGCTTCCCCTTCAACACCAGCGTGGTGTACAAG
	LeuProValAspAlaArgPheProProArgValProLysSerPheProPheAsnThrSerValValTyrLys
217	AAGACCCTGTTCGTGGAGTTCACCGACCACCTGTTCAACATCGCCAAGCCCCGCCCCCCTGGATGGGCCTG
	LysThrLeuPheValGluPheThrAspHisLeuPheAsnIleAlaLysProArgProProTrpMetGlyLeu
	Apal MscI
289	CTGGGCCCACCATCCAGGCCGAGGTGTACGACACCGTGGTGATCACCCTGAAGAACATGGCCAGCCA
91▶	LeuGlyProThrIleGlnAlaGluValTyrAspThrValValIleThrLeuLysAsnMetAlaSerHisPro
361	GTGAGCCTGCACGCCGTGGGCGTGAGCTACTGGAAGGCCAGCGAGGGCGCCGAGTACGACGACCAGACCAGC
115▶	ValSerLeuHisAlaValGlyValSerTyrTrpLysAlaSerGluGlyAlaGluTyrAspAspGlnThrSer
433	CAGCGCGAGAAGGAGGACGACAAGGTGTTCCCCGGCGGCAGCCACCCTACGTGTGGCAGGTGCTGAAGGAG
139▶	GlnArgGluLysGluAspAspLysValPheProGlyGlySerHisThrTyrValTrpGlnValLeuLysGlu
	MscI PmII
	AACGGCCCCATGGCCAGCGACCCCCTGTGCCTGACCTACAGCTACCTGAGCCACGTGGACCTGGTGAAGGAC
163▶	AsnGlyProMetAlaSerAspProLeuCysLeuThrTyrSerTyrLeuSerHisValAspLeuValLysAsp
	MscI
•	CTGAACAGCGGCCTGATCGGCGCCCTGCTGGTGTCCCGCGAGGGCAGCCTGGCCAAGGAGAAGACCCAGACC
	LeuAsnSerGlyLeuIleGlyAlaLeuLeuValCysArgGluGlySerLeuAlaLysGluLysThrGlnThr
	CTGCACAAGTTCATCCTGCTGTTCGCCGTGTTCGACGAGGGCAAGAGCTGGCACAGCGAGACCAAGAACAGC
	LeuHisLysPheIleLeuLeuPheAlaValPheAspGluGlyLysSerTrpHisSerGluThrLysAsnSer
	CTGATGCAGGACCGCGACGCCCAGCGCCCGCGCCTGGCCCAAGATGCACACCGTGAACGCTACGTGAAC
235	LeuMetGlnAspArgAspAlaAlaSerAlaArgAlaTrpProLysMetHisThrValAsnGlyTyrValAsn
502	PmII CGCAGCCTGCCCGGCTGATCGGCTGCCACCGCAAGAGCGTGTACTGGCACGTGATCGGCATGGGCACCACC
	ArgSerLeuProGlyLeuIleGlyCysHisArgLysSerValTyrTrpHisValIleGlyMetGlyThrThr
	CCCGAGGTGCACAGCATCTTCCTGGAGGGCCACACCTTCCTGGTGCGCAACCACCGCCAGGCCAGCCTGGAG
	ProGluValHisSerIlePheLeuGluGlyHisThrPheLeuValArgAsnHisArgGlnAlaSerLeuGlu
_	ATCAGCCCCATCACCTTCCTGACCGCCCAGACCCTGCTGATGGACCTGGGCCAGTTCCTGCTGTTCTGCCAC
<b>J L</b> .	IleSerProIleThrPheLeuThrAlaGlnThrLeuLeuMetAspLeuGlyGlnPheLeuLeuPheCysHis
	ATCAGCAGCCACCAGCACGACGGCATGGAGGCCTACGTGAAGGTGGACAGCTGCCCCGAGGAGCCCCCAGCTG
	IleSerSerHisGlnHisAspGlyMetGluAlaTyrValLysValAspSerCysProGluGluProGlnLeu
	CGCATGAAGAACAACGAGGAGGCCGAGGACTACGACGACGACCTGACCGACAGCGAGATGGACGTGCTGCCC
	ArgMetLysAsnAsnGluGluAlaGluAspTyrAspAspAspLeuThrAspSerGluMetAspValValArg
	(BgIII/BamHI)
1153	TTCGACGACGACAACAGCCCCAGCTTCATCCAGATCCGCAGCGTGGCCAAGAAGCACCCCAAGACCTGGGTG
	PheAspAspAspAsnSerProSerPheIleGlnIleArgSerValAlaLysLysHisProLysThrTrpVal
1225	CACTACATCGCCGCCGAGGAGGAGGACTGGGACTACGCCCCCTGGTGCTGGCCCCCGACGACCGCAGCTAC
	HisTyrIleAlaAlaGluGluAspTrpAspTyrAlaProLeuValLeuAlaProAspAspArgSerTyr
	Eagl
1297	AAGAGCCAGTACCTGAACAACGGCCCCCAGCGCATCGGCCGCAAGTACAAGAAGGTGCGCTTCATGGCCTAC
	LysSerGlnTyrLeuAsnAsnGlyProGlnArgIleGlyArgLysTyrLysLysValArgPheMetAlaTyr
	Apal
1369	ACCGACGAGACCTTCAAGACCCGCGAGGCCATCCAGCACGAGAGCGGCATCCTGGGCCCCCTGCTGTACGGC

451 ThraspGluThrPheLysThrargGluAlaIleGlnHisGluSerGlyIleLeuGlyProLeuLeuTyrGly

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- 1441 GAGGTGGGCGACACCCTGCTGATCATCTTCAAGAACCAGGCCAGCCGCCCCTACAACATCTACCCCCACGGC 475 GluValGlyAspThrLeuLeuIleIlePheLysAsnGlnAlaSerArgProTyrAsnIleTyrProHisGly 1513 ATCACCGACGTGCGCCCCTGTACAGCCGCCGCCTGCCCAAGGGCGTGAAGCACCTGAAGGACTTCCCCATC 499 IleThrAspValArgProLeuTyrSerArgArgLeuProLysGlyValLysHisLeuLysAspPheProIle
  - Balli
- 1585 CTGCCCGGCGAGATCTTCAAGTACAAGTGGACCGTGACCGTGGAGGACGGCCCCACCAAGAGCGACCCCCGC
- 523 LeuProGlyGluIlePheLysTyrLysTrpThrValThrValGluAspGlyProThrLysSerAspProArg
- 1657 TGCCTGACCCGCTACTACAGCAGCTTCGTGAACATGGAGCGCGACCTGGCCAGCGGCCTGATCGGCCCCCTG
- 547 CysLeuThrArgTyrTyrSerSerPheValAsnMetGluArgAspLeuAlaSerGlyLeuIleGlyProLeu
- 1729 CTGATCTGCTACAAGGAGAGCGTGGACCAGCGCGGCAACCAGATCATGAGCGACAAGCGCAACGTGATCCTG
- 571 LeuIleCysTyrLysGluSerValAspGlnArgGlyAsnGlnIleMetSerAspLysArgAsnValIleLeu

### Kpnl

- 1801 TTCAGCGTGTTCGACGAGAACCGCAGCTGGTACCTGACCGAGAACATCCAGCGCTTCCTGCCCAACCCCGCC
- 595 PheSerValPheAspGluAsnArgSerTrpTyrLeuThrGluAsnIleGlnArgPheLeuProAsnProAla
- 1873 GGCGTGCAGCTGGAGGACCCCGAGTTCCAGGCCAGCAACATCATGCACAGCATCAACGGCTACGTGTTCGAC
- 1945 AGCCTGCAGCTGAGCGTGTGCCTGCACGAGGTGGCCTACTGGTACATCCTGAGCATCGGCGCCCCAGACCGAC
- 643 SerLeuGlnLeuSerValCysLeuHisGluValAlaTyrTrpTyrIleLeuSerIleGlyAlaGlnThrAsp
- 2017 TTCCTGAGCGTGTTCTTCAGCGGCTACACCTTCAAGCACAAGATGGTGTACGAGGACACCCTGACCCTGTTC
- 667 PheLeuSerValPhePheSerGlyTyrThrPheLysHisLysMetValTyrGluAspThrLeuThrLeuPhe

#### <u>BamH</u>

- 691 ProPheSerGlyGluThrValPheMetSerMetGluAsnProGlyLeuTrpIleLeuGlyCysHisAsnSer
- 2161 GACTTCCGCAACCGCGGCATGACCGCCCTGCTGAAGGTGAGCAGCTGCGACAAGAACACCGGCGACTACTAC
- 715 AspPheArgAsnArgGlyMetThrAlaLeuLeuLysValSerSerCysAspLysAsnThrGlyAspTyrTyr
- $739 \blacktriangleright \texttt{GluAspSerTyrGluAspIleSerAlaTyrLeuLeuSerLysAsnAsnAlaIleGluProArgLeuGluGluBroArgLeuGluGluBroArgLeuGluGluBroArgLeuGluGluBroArgLeuGl$

#### **BstXI**

- 2305 ATCACCCGCACCACCCTGCAGAGCGACCAGGAGGAGATCGACTACGACGACACCATCAGCGTGGAGATGAAG
  - 763 IleThrArgThrThrLeuGlnSerAspGlnGluGluIleAspTyrAspAspThrIleSerValGluMetLys
- 2377 AAGGAGGACTTCGACATCTACGACGAGGACGAGAACCAGAGCCCCCGCAGCTTCCAGAAGAAGACCCGCCAC
- 787 LysGluAspPheAspIleTyrAspGluAspGluAsnGlnSerProArgSerPheGlnLysLysThrArgHis

#### Pmi

- 2449 TACTTCATCGCCGCCGTGGAGCGCCTGTGGGACTACGGCATGAGCAGCCCCCACGTGCTGCGCAACCGC
- 811 TyrPheIleAlaAlaValGluArgLeuTrpAspTyrGlyMetSerSerSerProHisValLeuArgAsnArg
- 2521 GCCCAGAGCGGCAGCGTGCCCCAGTTCAAGAAGGTGGTGTTCCAGGAGTTCACCGACGGCAGCTTCACCCAG
- $835 \blacktriangleright_{AlaGlnSerGlySerValProGlnPheLysLysValValPheGlnGluPheThrAspGlySerPheThrGln}$

#### Apal

- 2593 CCCCTGTACCGCGGCGAGCTGAACGAGCACCTGGGCCTGCTGGGCCCCTACATCCGCGCCGAGGTGGAGGAC
- 859 ProLeuTyrArgGlyGluLeuAsnGluHisLeuGlyLeuLeuGlyProTyrIleArgAlaGluValGluAsp

#### BstEll

- 2665 AACATCATGGTGACCTTCCGCAACCAGGCCAGCCGCCCCTACAGCTTCTACAGCAGCCTGATCAGCTACGAG
- 883 AsnIleMetValThrPheArgAsnGlnAlaSerArgProTyrSerPheTyrSerSerLeuIleSerTyrGlu
- 2737 GAGGACCAGCGCCAGGGCCCCGCAAGAACTTCGTGAAGCCCAACGAGACCAAGACCTACTTCTGG
- 907 GluAspGlnArgGlnGlyAlaGluProArgLysAsnPheValLysProAsnGluThrLysThrTyrPheTrp
- 2809 AAGGTGCAGCACCACATGGCCCCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCAGCGACGTG
- 931 LysValGlnHisHisMetAlaProThrLysAspGluPheAspCysLysAlaTrpAlaTyrPheSerAspVal

2881 GACCTGGAGAAGGACGTGCACAGCGGCCTGATCGGCCCCCTGCTGGTGTGCCACACCAACACCCTGAACCCC 955 AspLeuGluLysAspValHisSerGlyLeuIleGlyProLeuLeuValCysHisThrAsnThrLeuAsnPro **BstEll** 2953 GCCCACGGCCGCCAGGTGACCGTGCAGGAGTTCGCCCTGTTCTTCACCATCTTCGACGAGACCAAGAGCTGG 979 AlaHisGlyArgGlnValThrValGlnGluPheAlaLeuPhePheThrIlePheAspGluThrLysSerTrp 3025 TACTTCACCGAGAACATGGAGCGCAACTGCCGCGCCCCCTGCAACATCCAGATGGAGGACCCCACCTTCAAG 1003 TyrPheThrGluAsnMetGluArgAsnCysArgAlaProCysAsnIleGlnMetGluAspProThrPheLys 3097 GAGAACTACCGCTTCCACGCCATCAACGGCTACATCATGGACACCCTGCCCGGCCTGGTGATGGCCCAGGAC 1027 GluAsnTyrArgPheHisAlaIleAsnGlyTyrIleMetAspThrLeuProGlyLeuValMetAlaGlnAsp Pmli 3169 CAGCGCATCCGCTGGTACCTGCTGAGCATGGGCAGCAACGAGAACATCCACAGCATCCACTTCAGCGGCCAC 1051 GlnArgIleArgTrpTyrLeuLeuSerMetGlySerAsnGluAsnIleHisSerIleHisPheSerGlyHis 3241 GTGTTCACCGTGCGCAAGAAGGAGGAGTACAAGATGGCCCTGTACAACCTGTACCCCGGCGTGTTCGAGACC 1075 ValPheThrValArgLysLysGluGluTyrLysMetAlaLeuTyrAsnLeuTyrProGlyValPheGluThr 3313 GTGGAGATGCTGCCCAGCAAGGCCGGCATCTGGCGCGTGGAGTGCCTGATCGGCGAGCACCTGCACGCCGGC 1099 ValGluMetLeuProSerLysAlaGlyIleTrpArgValGluCysLeuIleGlyGluHisLeuHisAlaGly 3385 ATGAGCACCCTGTTCCTGGTGTACAGCAACAAGTGCCAGACCCCCCTGGGCATGGCCAGCGGCCACATCCGC 1123 MetSerThrLeuPheLeuValTyrSerAsnLysCysGlnThrProLeuGlyMetAlaSerGlyHisIleArg Apai 3457 GACTTCCAGATCACCGCCAGCGGCCAGTACGGCCAGTGGGCCCCCAAGCTGGCCCGCCTGCACTACAGCGGC 1147 AspPheGlnIleThrAlaSerGlyGlnTyrGlyGlnTrpAlaProLysLeuAlaArgLeuHisTyrSerGly 3529 AGCATCAACGCCTGGAGCACCAAGGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCCCATGATCATC 1171 SerileAsnAlaTrpSerThrLysGluProPheSerTrpIleLysValAspLeuLeuAlaProMetIleIle 3601 CACGGCATCAAGACCCAGGGCGCCCGCCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATCATGTAC 1195 hisGlyIleLysThrGlnGlyAlaArgGlnLysPheSerSerLeuTyrIleSerGlnPheIleIleMetTyr 3673 AGCCTGGACGGCAAGAAGTGGCAGACCTACCGCGGCAACAGCACCGGCACCCTGATGGTGTTCTTCGGCAAC 1219 SerLeuAspGlyLysLysTrpGlnThrTyrArgGlyAsnSerThrGlyThrLeuMetValPhePheGlyAsn (Smal/EcoRV) 3745 GTGGACAGCGGCATCAAGCACAACATCTTCAACCCCCCCATCATCGCCCGCTACATCCGCCTGCACCCC 1243 ValAspSerSerGlyIleLysHisAsnIlePheAsnProProIleIleAlaArgTyrIleArgLeuHisPro 3817 ACCCACTACAGCATCCGCAGCACCCTGCGCATGGAGCTGATGGGCTGCGACCTGAACAGCTGCAGCATGCCC 1267 ThrHisTyrSerIleArgSerThrLeuArgMetGluLeuMetGlyCysAspLeuAsnSerCysSerMetPro 3889 CTGGGCATGGAGAGCCAACGCCATCAGCGACGCCCAGATCACCGCCAGCAGCTACTTCACCAACATGTTCGCC 1291 LeuGlyMetGluSerLysAlaIleSerAspAlaGlnIleThrAlaSerSerTyrPheThrAsnMetPheAla 3961 ACCTGGAGCCCCAGCAAGGCCCGCCTGCACCTGCAGGGCCGCAGCAACGCCTGGCGCCCCCAGGTGAACAAC 1315 ThrTrpSerProSerLysAlaArgLeuHisLeuGlnGlyArgSerAsnAlaTrpArgProGlnValAsnAsn 4033 CCCAAGGAGTGGCTGCAGGTGGACTTCCAGAAGACCATGAAGGTGACCGGCGTGACCACCCAGGGCGTGAAG 1339 ProLysGluTrpLeuGlnValAspPheGlnLysThrMetLysValThrGlyValThrThrGlnGlyValLys 4105 AGCCTGCTGACCAGCATGTACGTGAAGGAGTTCCTGATCAGCAGCAGCCAGGACGGCCACCAGTGGACCCTG 1363 SerLeuLeuThrSerMetTyrValLysGluPheLeuIleSerSerSerGlnAspGlyHisGlnTrpThrLeu 4177 TTCTTCCAGAACGGCAAGGTGAAGGTGTTCCAGGGCAACCAGGACAGCTTCACCCCCGTGGTGAACAGCCTG 1387 PhePheGlnAsnGlyLysValLysValPheGlnGlyAsnGlnAspSerPheThrProValValAsnSerLeu 4249 GACCCCCCCTGCTGACCCGCTACCTGCGCATCCACCCCCAGAGCTGGGTGCACCAGATCGCCCTGCGCATG 1411 AspProProLeuLeuThrArgTyrLeuArgIleHisProGlnSerTrpValHisGlnIleAlaLeuArgMet

SmaI Hindill

4321 GAGGTGCTGGGCTGCGAGGCCCAGGACCTGTACTAGCTGCCCGGGCTACAAGCTTT

1435 GluValLeuGlyCysGluAlaGlnAspLeuTyr • • •

FIG. 7C

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BamHI E8 E

CATCTTAAGCCTAGGACCCGACGGTGTTGTCGCTGAAGGCGTTGGCGCCGTACTGGCGGGACGACTTCCACTCGTCGACGCTGTTCTTGTGGCCGCTGATGATG

AM8R4 GTAGAATTCGGATCCTGGGCTGCCACAACAGCGACTTCCGCAACCGCGGCATGACCGCCCTGCTGAAGGTGAGCTGCGGCGGCGACAAGAACACCGGCGACAACTACTAC

AM8F1

AM8FR2

3. OH 5' P

3. OH 5. P

CGCTGGTCCTCCTCTAGCTGATGCTGCTGGTAGTCGCACCTTCGAAATG GCGACCAGGAGGAGATCGACTACGACGACACCATCAGCGTGGAAGCTTTAC **Bst XI** AM8F4

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	E∞RI Nhel	
1	TAGAATTCGTAGGCTAGCATGCAGATCGAGCTGAGCACCTG	CTTCTTCCTGTGCCTGCTGCGCTTCTGCTTC
	_	sPhePheLeuCysLeuLeuArgPheCysPhe
73	AGCGCCACCCGCCGCTACTACCTGGGCGCCGTGGAGCTGAG	CTGGGACTACATGCAGAGCGACCTGGGCGAG
19▶	SerAlaThrArgArgTyrTyrLeuGlyAlaValGluLeuSe	rTrpAspTyrMetGlnSerAspLeuGlyGlu
145	CTGCCCGTGGACGCCCGCTTCCCCCCCCGCGTGCCCAAGAG	CTTCCCCTTCAACACCAGCGTGGTGTACAAG
43	LeuProValAspAlaArgPheProProArgValProLysSe	rPheProPheAsnThrSerValValTyrLys
217	AAGACCCTGTTCGTGGAGTTCACCGACCACCTGTTCAACAT	CGCCAAGCCCCGCCCCCTGGATGGGCCTG
	LysThrLeuPheValGluPheThrAspHisLeuPheAsnIl	eAlaLysProArgProProTrpMetGlyLeu
	Apal	MscI
289	CTGGGCCCCACCATCCAGGCCGAGGTGTACGACACCGTGGT	GATCACCCTGAAGAACATGGCCAGCCACCCC
	LeuGlyProThrIleGlnAlaGluValTyrAspThrValVa	llleThrLeuLysAsnMetAlaSerHisPro
361	GTGAGCCTGCACGCCGTGGGCGTGAGCTACTGGAAGGCCAG	GCGAGGGCGCCGAGTACGACGACCAGACCAGC
115	ValSerLeuHisAlaValGlyValSerTyrTrpLysAlaSe	erGluGlyAlaGluTyrAspAspGlnThrSer
433	CAGCGCGAGAAGGAGGACGACAAGGTGTTCCCCGGCGGCAG	CCACACCTACGTGTGGCAGGTGCTGAAGGAG
	GlnArgGluLysGluAspAspLysValPheProGlyGlySe	
	Msci	Pmil
505	AACGGCCCCATGGCCAGCGACCCCCTGTGCCTGACCTACAC	CTACCTGAGCCACGTGGACCTGGTGAAGGAC
163	▶ AsnGlyProMetAlaSerAspProLeuCysLeuThrTyrSe	erTyrLeuSerHisValAspLeuValLysAsp
		Mscl
	CTGAACAGCGGCCTGATCGGCGCCCTGCTGGTGTGCCGCGA	
187	▶ LeuAsnSerGlyLeuIleGlyAlaLeuLeuValCysArgGl	
649	CTGCACAAGTTCATCCTGCTGTTCGCCGTGTTCGACGAGGC	
	▶ LeuHisLysPheIleLeuLeuPheAlaValPheAspGluGl	
	CTGATGCAGGACCGCGACGCCCAGCGCCCGCGCCTGGCC	
235	▶ LeuMetGlnAspArgAspAlaAlaSerAlaArgAlaTrpPi	roLysMetHisThrValAsnGlyTyrValAsn
		Pmii
793	CGCAGCCTGCCCGGCCTGATCGGCTGCCACCGCAAGAGCG	
259	▶ ArgSerLeuProGlyLeuIleGlyCysHisArgLysSerVa	
865		
283	▶ ProGluValHisSerIlePheLeuGluGlyHisThrPheLe	
937		
	▶ IleSerProIleThrPheLeuThrAlaGlnThrLeuLeuMe	
L009	ATCAGCAGCCACCAGCACGACGCATGGAGGCCTACGTGA	AGGTGGACAGCTGCCCGAGGAGCCCCAGCTG
	▶ IleSerSerHisGlnHisAspGlyMetGluAlaTyrValL	
L081	CGCATGAAGAACAACGAGGAGGAGGACTACGACGACGA	ACCTGACCGACAGCGAGATGGACGTGGTGCGC
355 <b>l</b>	▶ ArgMetLysAsnAsnGluGluAlaGluAspTyrAspAspA	spLeuThrAspSerGluMetAspValValArg
,	(Bgill/Ban	
L153	TTCGACGACGACAACAGCCCCAGCTTCATCCAGATCCGCAG	GCGTGGCCAAGAAGCACCCCAAGACCTGGGTG
	▶ PheAspAspAspAsnSerProSerPheIleGlnIleArgS	
1225	CACTACATCGCCGCCGAGGAGGAGGACTGGGACTACGCCC	CCCTGGTGCTGGCCCCCGACGACCGCAGCTAC
403	HisTyrIleAlaAlaGluGluGluAspTrpAspTyrAlaP	roLeuValLeuAlaProAspAspArgSerTyr
	Eagl .	
1297	AAGAGCCAGTACCTGAACAACGGCCCCCAGCGCATCGGCC	GCAAGTACAAGAAGGTGCGCTTCATGGCCTAC
	▶ t.vsSerGlnTyrLeuAsnAsnGlyProGlnArgIleGlyA:	

1369 ACCGACGAGACCTTCAAGACCCGCGAGGCCATCCAGCACGAGAGCGGCATCCTGGGCCCCCTGCTGTACGGC 451 ThraspGluThrPheLysThrArgGluAlaIleGlnHisGluSerGlyIleLeuGlyProLeuLeuTyrGly

Apai

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1441 GAGGTGGGCGACACCCTGCTGATCATCTTCAAGAACCAGGCCAGCCGCCCCTACAACATCTACCCCCACGGC 475▶GluValGlyAspThrLeuLeuIleIlePheLysAsnGlnAlaSerArgProTyrAsnIleTyrProHisGly 1513 ATCACCGACGTGCGCCCCTGTACAGCCGCCGCCTGCCCAAGGGCGTGAAGCACCTGAAGGACTTCCCCATC 499▶ IleThrAspValArgProLeuTyrSerArgArgLeuProLysGlyValLysHisLeuLysAspPheProIle 1585 CTGCCCGGCGAGATCTTCAAGTACAAGTGGACCGTGACCGTGGAGGACGGCCCCACCAAGAGCGACCCCCGC 523 LeuProGlyGluIlePheLysTyrLysTrpThrValThrValGluAspGlyProThrLysSerAspProArg 1657 TGCCTGACCCGCTACTACAGCAGCTTCGTGAACATGGAGCGCGACCTGGCCAGCGGCCTGATCGGCCCCCTG 547 CysLeuThrArgTyrTyrSerSerPheValAsnMetGluArgAspLeuAlaSerGlyLeuIleGlyProLeu 1729 CTGATCTGCTACAAGGAGAGCGTGGACCAGCGCGCGAACCAGATCATGAGCGACAAGCGCAACGTGATCCTG 571 LeuIleCysTyrLysGluSerValAspGlnArgGlyAsnGlnIleMetSerAspLysArgAsnValIleLeu 1801 TTCAGCGTGTTCGACGAGAACCGCAGCTGGTACCTGACCGAGAACATCCAGCGCTTCCTGCCCAACCCCGCC 595 PheSerValPheAspGluAsnArgSerTrpTyrLeuThrGluAsnIleGlnArgPheLeuProAsnProAla 1873 GGCGTGCAGCTGGAGGACCCCGAGTTCCAGGCCAGCAACATCATGCACAGCATCAACGGCTACGTGTTCGAC 619 GlyValGlnLeuGluAspProGluPheGlnAlaSerAsnIleMetHisSerIleAsnGlyTyrValPheAsp 1945 AGCCTGCAGCTGAGCGTGTCCCTGCACGAGGTGGCCTACTGGTACATCCTGAGCATCGGCGCCCAGACCGAC 643 SerLeuGlnLeuSerValCysLeuHisGluValAlaTyrTrpTyrIleLeuSerIleGlyAlaGlnThrAsp 2017 TTCCTGAGCGTGTTCTTCAGCGGCTACACCTTCAAGCACAAGATGGTGTACGAGGACACCCTGACCCTGTTC 667 PheLeuSerValPhePheSerGlyTyrThrPheLysHisLysMetValTyrGluAspThrLeuThrLeuPhe 2089 CCCTTCAGCGGCGAGACCGTGTTCATGAGCATGGAGAACCCCGGCCTGTGGATCCTGGGCTGCCACAACAGC 691 propheSerGlyGluThrValPheMetSerMetGluAsnProGlyLeuTrpIleLeuGlyCysHisAsnSer 2161 GACTTCCGCAACCGCGGCATGACCGCCCTGCTGAAGGTGAGCAGCTGCGACAAGAACACCGGCGACTACTAC  $715 \blacktriangleright \texttt{AspPheArgAsnArgGlyMetThrAlaLeuLeuLysValSerSerCysAspLysAsnThrGlyAspTyrTyr}$ 2233 GAGGACAGCTACGAGGACATCAGCGCCTACCTGCTGAGCAAGAACAACGCCATCGAGCCC<u>CGCAGGCGCAGG</u> 739 GluAspSerTyrGluAspIleSerAlaTyrLeuLeuSerLysAsnAsnAlaIleGluProArgArgArgArg 2305 CGCGAGATCACCCGCACCACCCTGCAGAGCGACCAGGAGGAGATCGACTACGACGACACCATCAGCGTGGAG 763 ArgGluIleThrArgThrThrLeuGlnSerAspGlnGluGluIleAspTyrAspAspThrIleSerValGlu 2377 ATGAAGAAGGAGGACTTCGACATCTACGACGAGGACGAGAACCAGAGCCCCCGCAGCTTCCAGAAGAAGACC 787 MetLysLysGluAspPheAspIleTyrAspGluAspGluAsnGlnSerProArgSerPheGlnLysLysThr 2449 CGCCACTACTTCATCGCCGCCGTGGAGCGCCTGTGGGACTACGGCATGAGCAGCCCCCACGTGCTGCGC 811 ArghisTyrPheIleAlaAlaValGluArgLeuTrpAspTyrGlyMetSerSerProHisValLeuArg 2521 AACCGCGCCCAGAGCGGCAGCGTGCCCCAGTTCAAGAAGGTGGTGTTCCAGGAGTTCACCGACGGCAGCTTC 835 AsnArgAlaGlnSerGlySerValProGlnPheLysLysValValPheGlnGluPheThrAspGlySerPhe Apal 2593 ACCCAGCCCTGTACCGCGGGGGGCTGAACGAGCACCTGGGCCTGCTGGGCCCCTACATCCGCGCCGAGGTG 859 ThrGlnProLeuTyrArgGlyGluLeuAsnGluHisLeuGlyLeuLeuGlyProTyrIleArgAlaGluVal 2665 GAGGACAACATCATGGTGACCTTCCGCAACCAGGCCAGCCGCCCCTACAGCTTCTACAGCAGCCTGATCAGC 883 DGluAspAsnIleMetValThrPheArgAsnGlnAlaSerArgProTyrSerPheTyrSerSerLeuIleSer 2737 TACGAGGAGCACCAGCGCCCAGGCCCCGCAAGAACTTCGTGAAGCCCAACGAGACCAAGACCTAC  $907 \blacktriangleright \texttt{TyrGluGluAspGlnArgGlnGlyAlaGluProArgLysAsnPheValLysProAsnGluThrLysThrTyr}$ 2809 TTCTGGAAGGTGCAGCACCACATGGCCCCCACCAAGGACGAGTTCGACTGCAAGGCCTGGGCCTACTTCAGC

931 PheTrpLvsValGlnHisHisMetAlaProThrLvsAspGluPheAspCvsLvsAlaTrpAlaTvrPheSer

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2881 GACGTGGACCTGGAGAAGGACGTGCACAGCGGCCTGATCGGCCCCCTGCTGGTGTGCCACACCACCACCCTG 955 AspValAspLeuGluLysAspValHisSerGlyLeuIleGlyProLeuLeuValCysHisThrAsnThrLeu 2953 AACCCCGCCCACGGCCAGGTGACCGTGCAGGAGTTCGCCCTGTTCTTCACCATCTTCGACGAGACCAAG 979 AsnProAlaHisGlyArgGlnValThrValGlnGluPheAlaLeuPhePheThrIlePheAspGluThrLys 3025 AGCTGGTACTTCACCGAGAACATGGAGCGCAACTGCCGCGCCCCTGCAACATCCAGATGGAGGACCCCACC 1003 SerTrpTyrPheThrGluAsnMetGluArgAsnCysArgAlaProCysAsnIleGlnMetGluAspProThr 3097 TTCAAGGAGAACTACCGCTTCCACGCCATCAACGGCTACATCATGGACACCCTGCCCGGCCTGGTGATGGCC 1027 PheLysGluAsnTyrArgPheHisAlaIleAsnGlyTyrIleMetAspThrLeuProGlyLeuValMetAla Kpnl 3169 CAGGACCAGCGCATCCGCTGGTACCTGCTGAGCATGGGCAGCAACGAGAACATCCACAGCATCCACTTCAGC 1051 GlnAspGlnArgIleArgTrpTyrLeuLeuSerMetGlySerAsnGluAsnIleHisSerIleHisPheSer 3241 GGCCACGTGTTCACCGTGCGCAAGAAGGAGGAGTACAAGATGGCCCTGTACAACCTGTACCCCGGCGTGTTC 1075 GlyHisValPheThrValArgLysLysGluGluTyrLysMetAlaLeuTyrAsnLeuTyrProGlyValPhe 3313 GAGACCGTGGAGATGCTGCCCAGCAAGGCCGGCATCTGGCGCGTGGAGTGCCTGATCGGCGAGCACCTGCAC 1099 GluThrValGluMetLeuProSerLysAlaGlyIleTrpArgValGluCysLeuIleGlyGluHisLeuHis 3385 GCCGGCATGAGCACCCTGTTCCTGGTGTACAGCAACAAGTGCCAGACCCCCCTGGGCATGGCCAGCGCCAC 1123 AlaGlyMetSerThrLeuPheLeuValTyrSerAsnLysCysGlnThrProLeuGlyMetAlaSerGlyHis Apai 3457 ATCCGCGACTTCCAGATCACCGCCAGCGGCCAGTACGGCCAGTGGGCCCCCAAGCTGCCCCGCCTGCACTAC 1147 IleArgAspPheGlnIleThrAlaSerGlyGlnTyrGlyGlnTrpAlaProLysLeuAlaArgLeuHisTyr 3529 AGCGGCAGCATCAACGCCTGGAGCACCAAGGAGCCCTTCAGCTGGATCAAGGTGGACCTGCTGGCCCCCATG 1171 SerGlySerIleAsnAlaTrpSerThrLysGluProPheSerTrpIleLysValAspLeuLeuAlaProMet 3601 ATCATCCACGGCATCAAGACCCAGGGCGCCCCAGAAGTTCAGCAGCCTGTACATCAGCCAGTTCATCATC 1195 IleIleHisGlyIleLysThrGlnGlyAlaArgGlnLysPheSerSerLeuTyrIleSerGlnPheIleIle 3673 ATGTACAGCCTGGACGGCAAGAAGTGGCAGACCTACCGCGGCAACAGCACCGGCACCCTGATGGTGTTCTTC 1219 MetTyrSerLeuAspGlyLysLysTrpGlnThrTyrArgGlyAsnSerThrGlyThrLeuMetValPhePhe (Smal/EcoRV) 3745 GGCAACGTGGACAGCAGCGCCATCAAGCACAACATCTTCAACCCCCCCATCATCGCCCGCTACATCCGCCTG 1243 GlyAsnValAspSerSerGlyIleLysHisAsnIlePheAsnProProIleIleAlaArgTyrIleArgLeu 3817 CACCCCACCACTACAGCATCCGCAGCACCCTGCGCATGGAGCTGATGGGCTGCGACCTGAACAGCTGCAGC 1267 HisProThrHisTyrSerIleArgSerThrLeuArgMetGluLeuMetGlyCysAspLeuAsnSerCysSer 3889 ATGCCCCTGGGCATGGAGAGCAAGGCCATCAGCGACGCCCAGATCACCGCCAGCAGCTACTTCACCAACATG 1291 MetProLeuGlyMetGluSerLysAlaIleSerAspAlaGlnIleThrAlaSerSerTyrPheThrAsnMet 3961 TTCGCCACCTGGAGCCCCAGCAAGGCCCGCCTGCACCTGCAGGGCCGCAGCAACGCCTGGCGCCCCCAGGTG 1315 PheAlaThrTrpSerProSerLysAlaArgLeuHisLeuGlnGlyArgSerAsnAlaTrpArgProGlnVal 4033 AACAACCCCAAGGAGTGGCTGCAGGTGGACTTCCAGAAGACCATGAAGGTGACCGGCGTGACCACCCAGGGC 1339 AsnAsnProLysGluTrpLeuGlnValAspPheGlnLysThrMetLysValThrGlyValThrThrGlnGly 4105 GTGAAGAGCCTGCTGACCAGCATGTACGTGAAGGAGTTCCTGATCAGCAGCAGCCAGGACGGCCACCAGTGG 1363 ValLysSerLeuLeuThrSerMetTyrValLysGluPheLeuIleSerSerSerGlnAspGlyHisGlnTrp 4177 ACCCTGTTCTTCCAGAACGGCAAGGTGAAGGTGTTCCAGGGCAACCAGGACAGCTTCACCCCCGTGGTGAAC 1387 ThrLeuPhePheGlnAsnGlyLysValLysValPheGlnGlyAsnGlnAspSerPheThrProValValAsn 4249 AGCCTGGACCCCCCTGCTGACCCGCTACCTGCGCATCCACCCCCAGAGCTGGGTGCACCAGATCGCCCTG 1411 SerLeuAspProProLeuLeuThrArgTyrLeuArgIleHisProGlnSerTrpValHisGlnIleAlaLeu

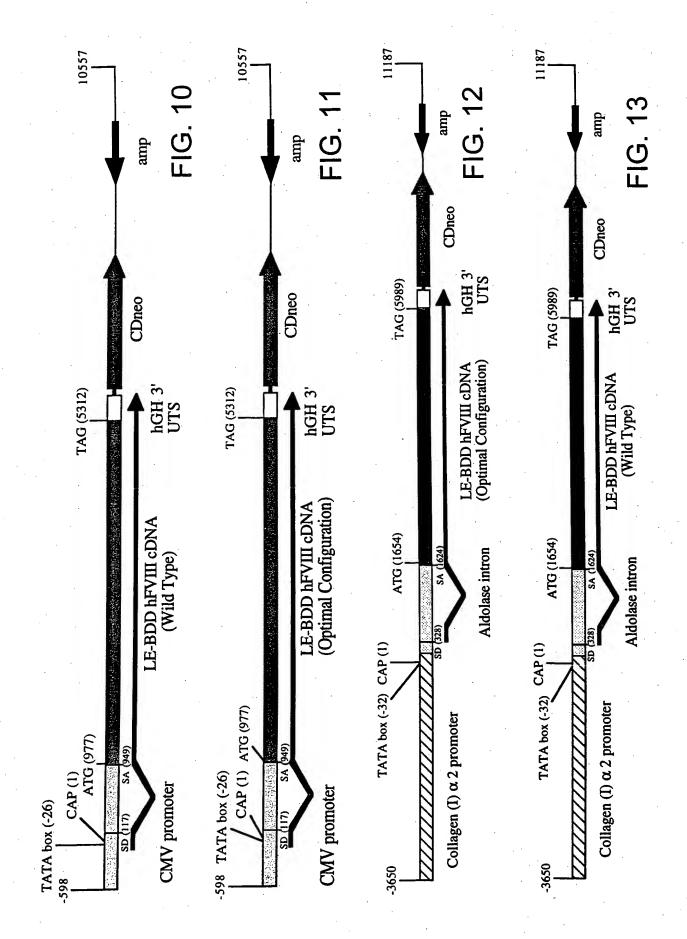
4321 CGCATGGAGGTGCTGGGCTGCGAGGCCCAGGACCTGTACTAGCTGCCCGGGCTACAAGCTTTAC

1435 ArgMetGluValLeuGlyCysGluAlaGlnAspLeuTyr...

FIG. 9C

Hindlll

SmaI



### Codon Frequency in Highly Expressed Human Genes

	% oc	currence	% occurrence			% occurrence		
<u>Glu</u>			Cys			Gln		•
GA	Α	25	TG	C	68	CA	A	12
	G	75	•	<b>T</b> .	32		G	88
					•			
Arg			<u>Ala</u>	٠٠.	-	<u>Gly</u>	. :	•
CG	C	37	GC	C	53	GG	C	50
	<b>T</b> .	7		<b>T</b> .	17		T	12
• • •	Α	6		A	13	•	Α	14
	G	21		G ·	17		G	24
AG	Α	10			. •		:	
٠	G	18			*			
							٠.	
Leu			<u>Ser</u>			<u>Pro</u>		
CT	C	26	TC	C	28	CC	$\mathbf{C}$	48
	T	5		T	13		T	19
	A	3		Α	5		A	16
	G	58		G	9		G	17
TT	Α	2	AG	C	34		٠.	
	G	6	-	$\mathbf{T}$	10	•		
						•		

FIG. 14A

### Codon Frequency in Highly Expressed Human Genes

% occurrence			·	% occurrence			% occurrence		
<u>Ilc</u>			<u>Thr</u>			<u>Val</u>			:
AT	C	77	AC	C	57	GT	С	25	
	$\mathbf{T}^{\mathbf{T}}$	18		T	14	·	$\dot{\mathbf{T}}$	7	•
	Α	5		Α	14		A	5	
		*		G	15		G	64	
<u>Tyr</u>		*	Phe			<u>Lys</u>	:		,
TA	C	74	TT	$\mathbf{C}^{\cdot}$	80	AA	A	18	
·	T	26	·	T	20		G	82	
Asn			<u>His</u>			÷		•	
AA	C	78	CA	C	79	•			
	T	25		T	21				* .
			•					·	

FIG. 14B

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